Eur J Vasc Endovasc Surg **19**, 356–361 (2000)
doi:10.1053/ejvs.1999.1010, available online at http://www.idealibrary.com on IDEAL®

Carotid Atherosclerosis in Relation to Symptoms from the Territory Supplied by the Carotid Artery

S. Hallerstam[1], C. Carlström[2], M. Zetterling[2], P. Konrad[3] and S. Rosfors*[1]

Karolinska Institutet, Stockholm, Sweden: Departments of [1]Clinical Physiology, [2]Medicine and [3]Surgery at Stockholm Söder Hospital, Stockholm, Sweden

Objectives: *to investigate the relationship between intima–media thickness in the common carotid artery, plaque morphology in the carotid bifurcation and symptoms of cerebral embolism.*
Design: *prospective study of consecutive patients referred for carotid duplex examination.*
Methods: *One hundred and eighty-eight patients were classified by one of two neurologists into four categories (symptomatic, asymptomatic, undefined, uncertain). Carotid atherosclerosis was measured by means of high-resolution ultrasound technique. Carotid plaques were classified based on visual evaluation of plaque echogenicity.*
Results: *intima–media thickness (IMT) was correlated to presence of plaques, age and gender, but not to symptoms referable to the carotid circulation. Carotid plaques were more common in symptomatic than in asymptomatic vessels ($p<0.05$). There was no difference in plaque occurrence between the ipsi- and contralateral sides in the symptomatic patients, neither in frequency of echolucent plaques between the sides or between symptomatic and asymptomatic patients. Echogenic plaques were more common and generally smaller than echolucent plaques.*
Conclusions: *IMT correlates with presence of plaques, but not with symptoms from the territory supplied by the carotid artery. Echolucent plaques in the carotid bifurcation are not more frequently symptomatic than echogenic plaques are, in patients with low-to-moderate degree of carotid stenosis.*

Key Words: Ultrasonography; Intima–media thickness; Plaque echogenicity; Cerebral embolism.

Introduction

Increased thickness of the inner layer of the arterial wall (intima–media) constitutes an early sign of atherosclerosis. Intima–media thickness (IMT) in the carotid arteries can be measured by non-invasive high-resolution ultrasound, and increased wall thickness has been used as a marker of general atherosclerosis. An increased IMT, measured in the distal common carotid artery (CCA), has been shown to be an independent predictor of future cardiac and cerebral ischaemic events.[1,2]

It is well known that the degree of stenosis is of importance[3,4] regarding carotid stenosis and its relationship to cerebral symptoms (transient ischaemic attacks/stroke). Several investigations have also indicated that plaque morphology is important and that the appearance of echolucent plaques (evaluated by ultrasound B-mode imaging) imply an increased risk for cerebral or retinal embolisation.[5–7] It is still unclear whether this is also true for echolucent plaques without stenosis or in cases of low/moderate degrees of carotid stenosis. We have recently shown a significant relationship between IMT in the common carotid artery and the presence of atherosclerotic plaques in the carotid bifurcation.[8] The present study further evaluates the relationship between IMT/plaque morphology and symptoms from the territory supplied by the carotid artery in a consecutive series of patients referred for carotid duplex examination.

Material and Methods

All patients referred for carotid duplex scanning to the Vascular Laboratory at the Department of Clinical Physiology at Stockholm Söder Hospital during a 2-month period ($n=192$) were entered in a prospective study of carotid vessel-wall disease approved by the local ethic committee. Patients seen after carotid endarterectomy ($n=4$) were excluded. The remaining 188 patients were classified by one of two neurologists

* Please address all correspondence to: S. Rosfors, Department of Clinical Physiology, Stockholm Söder Hospital, S-118 83 Stockholm, Sweden.

according to presence or absence of symptoms from the territory supplied by the carotid artery. The patients were divided into four categories:

1. *Symptomatic*, $n = 81$. Seventy-two patients had ipsilateral hemispheric symptoms, eight had ipsilateral amaurosis fugax and one patient had both ipsilateral hemispheric symptoms and ipsilateral amaurosis fugax.
2. *Asymptomatic*, $n = 69$. Fifty patients were referred for evaluation of different "cerebral symptoms" from territories not supplied by the carotid artery (e.g. vertigo, unspecific visual disorders, transient periods of absence, headache) with or without a carotid bruit, 17 patients were referred for evaluation of a carotid bruit without any other symptoms, and two patients were referred prior to cardiac surgery.
3. *Undefined*, $n = 17$. Symptomatic patients, but with symptoms from territories that partly might be supplied by the carotid artery. These patients could then not reliably be classified as symptomatic or asymptomatic regarding the carotid circulation and they were consequently not used for any further analyses. One patient with bilateral symptoms was also referred to this group.
4. *Uncertain*, $n = 21$. These patients were not seen by a neurologist and the patients' chart could not provide enough information to make a certain classification.

Groups 1 and 2 were further analysed regarding presence of plaques and IMT. We also searched for risk factors for cerebrovascular disease (i.e. hypertension, ischaemic heart disease, diabetes mellitus, peripheral artery disease or blood lipid disorder) in the patients' records and in other examinations including ECG and echocardiography. The latter was performed in 48 of 81 (59%) of the symptomatic patients and in 31 of 69 (45%) of the asymptomatic patients (NS). Sixty-seven (83%) of the symptomatic patients and 29 (42%) of the asymptomatic patients were primarily referred from a neurologist ($p<0.001$). The remaining patients were classified on the basis of data from the patients' records.

Duplex ultrasonography

Colour-duplex ultrasound scanning was performed using 5- or 7-MHz linear-array transducers (Acuson 128XP, Mountain View, CA, U.S.A.). The carotid arteries were scanned and tape recordings were made

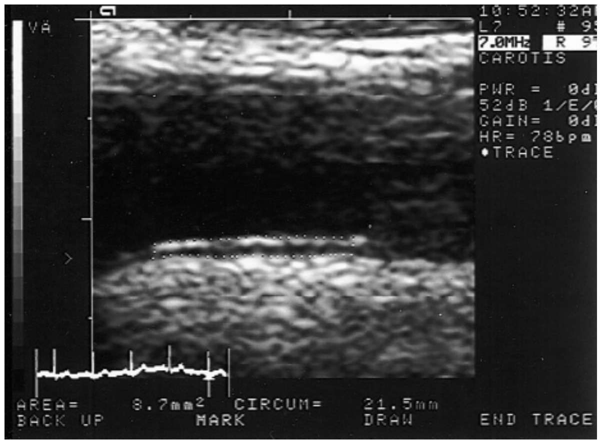

Fig. 1. Ultrasonographic image of measurement of intima–media thickness in the distal portion of the common carotid artery.

of vessel walls and blood-flow velocities in all segments. A blood-flow velocity above 1.2 m/s (or an occlusion with no flow) was used to define a stenosis with >50% lumen diameter reduction.[9,10]

The stenoses were graded as low (<1.2 m/s), moderate (1.2–3.5 m/s) and severe (>3.5 m/s) based on measurements of maximal blood-flow velocity. A moderate stenosis corresponds approximately with a diameter reduction of 50–75% and a severe stenosis with a diameter reduction of 76–99%.[9,11] An occlusion (100% stenosis) was diagnosed when there was no flow within the lumen of a visualised internal carotid artery and a low diastolic flow (close to zero) in the CCA.

At the end of the examination IMT was measured on both sides. The subject's head was tilted in order to achieve a horizontal access to the common carotid artery just proximal to the bulb. The 7-MHz probe was used together with the resolution box function of the system and settings were made to get an optimal picture of carotid walls. Magnified pictures were frozen incident with the R-wave on the electrocardiogram. Only the far walls of the artery were used for calculation. The IMT was defined as the distance between the leading edge of the luminal echo to the leading edge of the media/adventitia echo.[12] IMT was measured over 1-cm length just proximal to the bulb. This was accomplished by using a calliper and the trace function of the ultrasound system and calculation of the mean IMT over this length (Fig. 1). We never included plaques in the measurements (see definition below). IMT measurements are presented for each side separately or as IMT_{mean} (= right + left/2). At our laboratory, the coefficient of variation for intra- and interoperator variability for repeated examinations and measurements of IMT with this technique is 4.6% and 7.7%, respectively.[13]

A plaque was defined as >1 mm in diameter (=

protrusion into the vessel lumen) and >100% increase compared with the thickness of adjacent wall segments,[14] with a localisation to the carotid bifurcation or the proximal part of the internal carotid artery. Classification of ultrasound plaque appearance was performed independently from the videotape during a time-period of 2 weeks after inclusion of the last patient by one single operator blinded to all other data. We used the most common classification system, with five categories:[5–7]

(1) uniformly echolucent;
(2) dominantly echolucent with echolucent areas greater than 50%;
(3) dominantly echogenic with echogenic areas greater than 50%;
(4) uniformly echogenic and
(5) unclassified due to heavy calcification and acoustic shadowing.

Evaluation of intraoperator variability for plaque characterisation into five groups demonstrated a weighted k value of 0.75. For types 1–2 vs. types 3–4 the k value was 0.80.[8]

Statistical methods

Data are presented as mean and one standard deviation (S.D.). Paired or unpaired, two-sided Student's t-tests were used for comparison of IMT measures. The Chi-square test with Yates' correction was used for comparison of proportions. Multiple regression analyses were used to characterise relationships between variables. Statistical significance was inferred at $p<0.05$.

Results

The symptomatic and asymptomatic groups totalled 150 patients. Risk factors for cerebrovascular disease were found in 55% of these patients. Sixty-one per cent had a plaque in at least one of the carotid bifurcations and a >50% carotid stenosis was found in 25% of the patients. The two groups were comparable regarding age, gender, presence of risk factors and presence of plaques/stenoses in any of the carotid bifurcations. IMT_{mean} was also equal in the two groups (Table 1). In the symptomatic group of patients, we could not demonstrate any difference in plaque occurrence, presence of stenosis or the relative frequency of echolucent plaques between ipsi- and contralateral sides. IMT did not differ between the sides and neither (right or left) were more often symptomatic (Table 2).

A more detailed description of plaque morphology and its distribution in symptomatic and asymptomatic patients is shown in Table 3. In the 150 patients plaques were seen in 149 of 300 carotid bifurcations. Sixty per cent (49/81) of the symptomatic vessels, 47% (38/81)

Table 1. Characteristics of symptomatic ($n=81$) and asymptomatic patients ($n=69$).

	Symptomatic	Asymptomatic	p value
Age, mean (range)	66 (37–85)	68 (37–88)	0.22
Males/females	41/40	33/36	0.86
Patients with risk factors	48 (59%)	35 (51%)	0.38
Patients with plaques (any side)	53 (65%)	39 (57%)	0.34
Patients with stenoses* (any side)	19 (23%)	18 (26%)	0.80
IMT_{mean}, mm (S.D.)	0.83 (0.20)	0.88 (0.25)	0.25

p value from unpaired two-sided t-test or Chi-square analysis. IMT_{mean} = intima–media thickness of the right + left common carotid artery/2.
* Stenoses with more than 50% lumen diameter reduction.

Table 2. Characteristics of symptomatic patients ($n=81$).

	Symptomatic side	Contralateral side	p value
Right/left side	41/40	40/41	1.0
Presence of plaque	49	38	0.12
Echolucent/echogenic plaque	14/31	11/24	0.83
Presence of stenosis*	11	8	0.62
IMT, mm (S.D.)	0.86 (0.27)	0.81 (0.18)	0.25

p value from paired two-sided t-test or Chi-square analysis. IMT = intima–media thickness of the common carotid artery.
* Stenoses with more than 50% lumen diameter reduction.

Table 3. Comparison of carotid plaque morphology in 69 asymptomatic and 81 symptomatic patients.

Plaque type	Asymptomatic patients (138 vessels)	Symptomatic patients		Total
		Symptomatic vessels	Contralateral vessels	
1	9	6	6	21
2	15	8	5	28
3	19	14	7	40
4	14	17	17	48
5	5	4	3	12
Total	62	49	38	149

Plaque types: 1 = uniformly echolucent; 2 = dominantly echolucent with echolucent areas greater than 50%; 3 = dominantly echogenic with echogenic areas greater than 50%; 4 = uniformly echogenic; 5 = unclassified due to heavy calcification and acoustic shadowing.

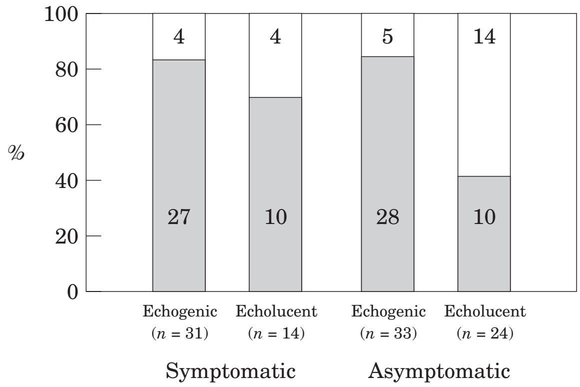

Fig. 2. Relative frequency of stenoses caused by echolucent (types 1–2) and echogenic plaques (types 3–4) in the symptomatic and the asymptomatic patient group. The number of plaques are given within the bars, unfilled areas represent plaques causing >50% stenosis and shaded areas represent plaques causing <50% stenosis. (□) >50% stenosis; (■) <50% stenosis.

Table 4. Comparison of carotid plaque morphology in asymptomatic and symptomatic patients with >50% carotid stenoses.

Plaque type	Asymptomatic patients	Symptomatic patients		Total
		Symptomatic vessels	Contralateral vessels	
1	5	2	1	8
2	9	2	2	13
3	4	2	1	7
4	1	2	2	5
5	3	3	2	8
Total	22	11	8	41

For plaque types, see Table 3.

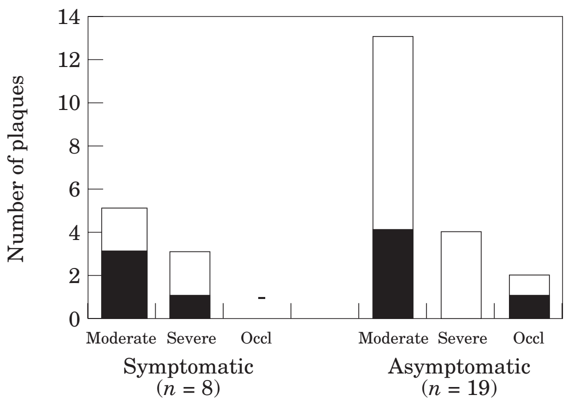

Fig. 3. The distribution of echolucent (types 1–2) and echogenic plaques (types 3–4) in relation to the degree of stenosis in symptomatic and asymptomatic patients. Moderate stenosis corresponds to approximately 50–75% diameter reduction and severe stenosis to >75%. Occl = occlusion. (□) Echolucent; (■) echogenic.

of contralateral vessels and 45% (62/138) of asymptomatic vessels contained plaques. The difference concerning plaque occurrence between symptomatic and asymptomatic vessels was statistically significant ($p<0.05$). Echogenic plaques (types 3–4) were generally more common than echolucent plaques (types 1–2) (88 vs. 49, $p<0.001$). In symptomatic vessels, as well as in contralateral vessels, 31% (14/45 and 11/35) of the plaques were echolucent. In the asymptomatic group 42% (24/57) of the plaques were echolucent ($p=0.35$ compared with symptomatic vessels).

A >50% stenosis was found in 14% (11/81) of the symptomatic vessels (10%, 8/81 on contralateral side) and in 16% (22/138) of the carotid bifurcations in the asymptomatic group. A stenosis was present in 43% (21/49) of the echolucent plaques and in 14% (12/88) of the echogenic plaques ($p<0.001$). The relative frequency of stenoses >50% caused by echolucent and echogenic plaques, respectively, is shown for both the symptomatic and the asymptomatic patient group in Figure 2. No significant difference regarding the relative frequency of echolucent/echogenic plaques between the groups was seen when the comparison was restricted to only those 41 vessels with plaques causing a >50% stenosis (Table 4).

Most of the 41 stenoses were of moderate degree, only eight of the plaques caused a severe degree of stenosis (flow velocity >3.5 m/s). Four of these eight were found in asymptomatic patients with echolucent plaques (2 type-1 and 2 type-2), three were found in symptomatic vessels (2 type-1 and 1 type-3) and one in a contralateral asymptomatic vessel with a type-1 plaque. Five of the 149 plaques caused a total occlusion of the internal carotid artery. Two of these were found in asymptomatic patients (1 type-2, 1 type-3), two were found in symptomatic vessels (type-5 plaques) and one type-5 plaque in a contralateral asymptomatic vessel. The distribution of echolucent and echogenic plaques in relation to the degree of stenosis is shown graphically in Figure 3.

In a multiple regression model with IMT_{mean} as dependent factor ($r=0.63$, $p<0.001$), there was a significant relation with age ($p<0.001$), gender ($p<0.001$) and presence of plaque ($p<0.001$), but not with symptoms. There was no relationship between IMT and plaque echogenicity. IMT on the symptomatic side was 0.94 (0.31) mm in symptomatic patients with plaques, compared with 0.99 (0.31) mm in asymptomatic patients with plaques (NS).

Discussion

We could not demonstrate any clear relationship between visual evaluation of plaque echolucency and symptoms from the territory supplied by the carotid artery, although we found echogenic plaques to be more common and generally smaller than echolucent plaques. Our results regarding plaque morphology fit well with those presented by Holdsworth *et al.*[15] They presented a large series of consecutive patients, with the main finding that carotid plaque morphology and degree of internal carotid stenosis are interrelated and, thus, mutually dependent factors. As the degree of stenosis increases, the plaque becomes more echolucent. Ultrasonographically echolucent areas are known to contain lipids and/or haemorrhage.[16] In the context of increased plaque size and increased echolucent areas, intraplaque haemorrhage might be a factor of importance. However, in the present study no effort was made to further characterise the echolucent areas.

Our results regarding cerebrovascular symptoms and the appearance of echolucent plaques contrast with some earlier reports. This is most probably due to the fact that we did not select patients with high-grade carotid stenoses. It appears from the literature that echolucent plaques causing severe degree of stenoses are unstable and symptomatic.[6,17,18] Earlier studies dealing with this topic have included symptomatic patients scheduled for carotid endarterectomy and groups of asymptomatic patients, in all cases with high-grade stenoses.[17,18] In one earlier study, patients selected for endarterectomy were compared with asymptomatic patients without specifying the degree of stenosis.[7] It is possible that the asymptomatic plaques were smaller and thus more echogenic. Cave *et al.*[5] showed results indicating that plaque echolucency is associated with patient symptoms. Nevertheless, it is important to consider that they had more stenoses in the symptomatic than in the asymptomatic group.

The thickness of the intima–media complex in the common carotid artery and its relationship to symptomatic cerebrovascular disease has not previously been described. In an earlier report we showed that IMT was related to both common markers of atherosclerosis and to the degree of atherosclerotic disease in the carotid bifurcation.[8] The lack of relationship between symptoms and IMT in the present study was not surprising. We suggest that IMT can be regarded as a marker for atherosclerosis, both general and in some parts even local, and that the association described earlier between IMT and cardiac[1] and cerebral morbidity[2] is due to the connection between progress of atherosclerosis in different vascular systems.

The relation between the atherosclerotic plaque in the carotid bifurcation and the process leading to cerebrovascular symptoms is most probably complex and of a multifactorial nature. One indisputably important factor is plaque size/degree of stenosis with increasing shear stresses on the arterial wall. This factor can be evaluated by modern ultrasonographic technique. Plaque echolucency is another factor that can be of importance; as stated above its relationship to symptomatic disease is so far documented only in connection with severe degree of carotid stenosis. Digital image processing with standardisation of the ultrasonic grey-scale image might increase the usefulness of plaque morphology analyses.[19,20] Plaque texture is an additional factor that is possibly of crucial importance. Ultrasonic evaluation of plaque texture is difficult and needs to be studied further using the most recent technology. Furthermore, we suggest that analyses of biochemical markers of haemostasis and inflammation can contribute to the understanding of the process starting the thromboembolic mechanism. Despite these sophisticated measures, one must realise that symptoms from the territory supplied by the carotid artery do not exclusively emanate from processes in the carotid bifurcation. Some symptomatic cases with low-to-moderate degree of stenosis might have a source of embolism in the heart or embolisation from a complicated plaque in the aortic arch, or the symptoms could alternatively originate from small-vessel occlusions due to lipohyalinosis of endarteries in the brain.

In summary, we found no relationship between plaque echogenicity and symptoms from the territory supplied by the carotid artery in our prospective series of patients, including mostly plaques causing low or moderate degrees of stenoses. The most striking finding was the association between plaque size and plaque echolucency. IMT in the common carotid artery was correlated to presence of plaques, age and gender, but not to cerebral symptoms from the territory supplied by the carotid artery.

Acknowledgements

This study was supported by grants from Karolinska Institutet, local funds at Stockholm Söder Hospital and Magnus Bergvall Foundation.

References

1 Chambless LE, Heiss G, Folsom AR *et al.* Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 1997; **146**: 483–494.

2 Bots ML. Wall thickness of the carotid artery as an indicator of generalised atherosclerosis: the Rotterdam study. Alblasserdam: Offsetdrukkerij Haveka BV, 1993.

3 North American Symptomatic Carotid Endarterectomy

Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis. *N Engl J Med* 1991; **325**: 445–453.
4 European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MCR European Carotid Surgery Trial (ECST). *Lancet* 1998; **351**: 1379–1387.
5 Cave EM, Pugh ND, Wilson RJ, Sissons GRJ, Woodcock JP. Carotid artery duplex scanning. Does plaque echogenicity correlate with patient symptoms? *Eur J Vasc Endovasc Surg* 1995; **100**: 77–81.
6 European Carotid Plaque Study Group. Carotid artery plaque composition – relationship to clinical presentation and ultrasound B-mode imaging. *Eur J Vasc Endovasc Surg* 1995; **10**: 23–30.
7 Steffen CM, Gray-Weale AC, Byrne KE, Lusby RJ. Carotid artery atheroma; ultrasound plaque appearance in symptomatic and asymptomatic vessels. *Austr NZ J Surg* 1989; **59**: 529–534.
8 Rosfors S, Hallerstam S, Jensen-Urstad K, Zetterling M, Carlström C. Relationship between intima-media thickness in the common carotid artery and atherosclerosis in the carotid bifurcation. *Stroke* 1998; **29**: 1378–1382.
9 Zbornikova V, Lassvik C, Johansson I. Prospective evaluation of the accuracy of duplex scanning with spectral analysis in carotid artery disease. *Clin Physiol* 1985; **5**: 257–269.
10 Robinson ML, Sacks D, Perlmutter GS, Marinelli DL. Diagnostic criteria for carotid duplex sonography. *AJR* 1988; **155**: 1045–1049.
11 Alexandrov AV, Brodie DS, McLean A *et al.* Correlation of peak systolic velocity and angiographic measurement of carotid stenosis revisited. *Stroke* 1997; **28**: 339–342.
12 Wendelhag I, Gustavsson T, Suurküla M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. *Clin Physiol* 1991; **11**: 565–577.
13 Jensen-Urstad K, Rosfors S. A methodological study of arterial wall function using ultrasound technique. *Clin Physiol* 1997; **17**: 557–567.
14 Lemne C, Jogestrand T, de Faire U. Carotid intima-media thickness and plaque in borderline hypertension. *Stroke* 1995; **26**: 34–39.
15 Holdsworth RJ, McCollum PT, Bryce JS, Harrison DK. Symptoms, stenosis and carotid plaque morphology. Is plaque morphology relevant? *Eur J Vasc Endovasc Surg* 1995; **9**: 80–85.
16 Reilly LM, Lusby RJ, Hughes L *et al.* Carotid plaque histology using real-time ultrasonography. *Am J Surg* 1983; **146**: 188–193.
17 Steinke W, Hennerici M, Rautenberg W, Mohr JP. Symptomatic and asymptomatic high-grade carotid stenoses in Doppler color-flow imaging. *Neurology* 1992; **42**: 131–138.
18 Geroulakos G, Ramaswami G, Nicolaides A *et al.* Characterisation of symptomatic and asymptomatic carotid plaques using high-resolution real-time ultrasonography. *Br J Surg* 1993; **80**: 1274–1277.
19 Elatrozy T, Nicolaides A, Tegos T *et al.* The effect of B-mode ultrasonic image standardisation on the echodensity of symptomatic and asymptomatic carotid bifurcation plaques. *Int Angiol* 1998; **17**: 179–186.
20 Biasi GM, Sampaolo A, Mingazzini P *et al.* Computer analysis of ultrasonic plaque echolucency in identifying high risk carotid bifurcation lesions. *Eur J Vasc Endovasc Surg* 1999; **17**: 476–479.

Accepted 18 October 1999